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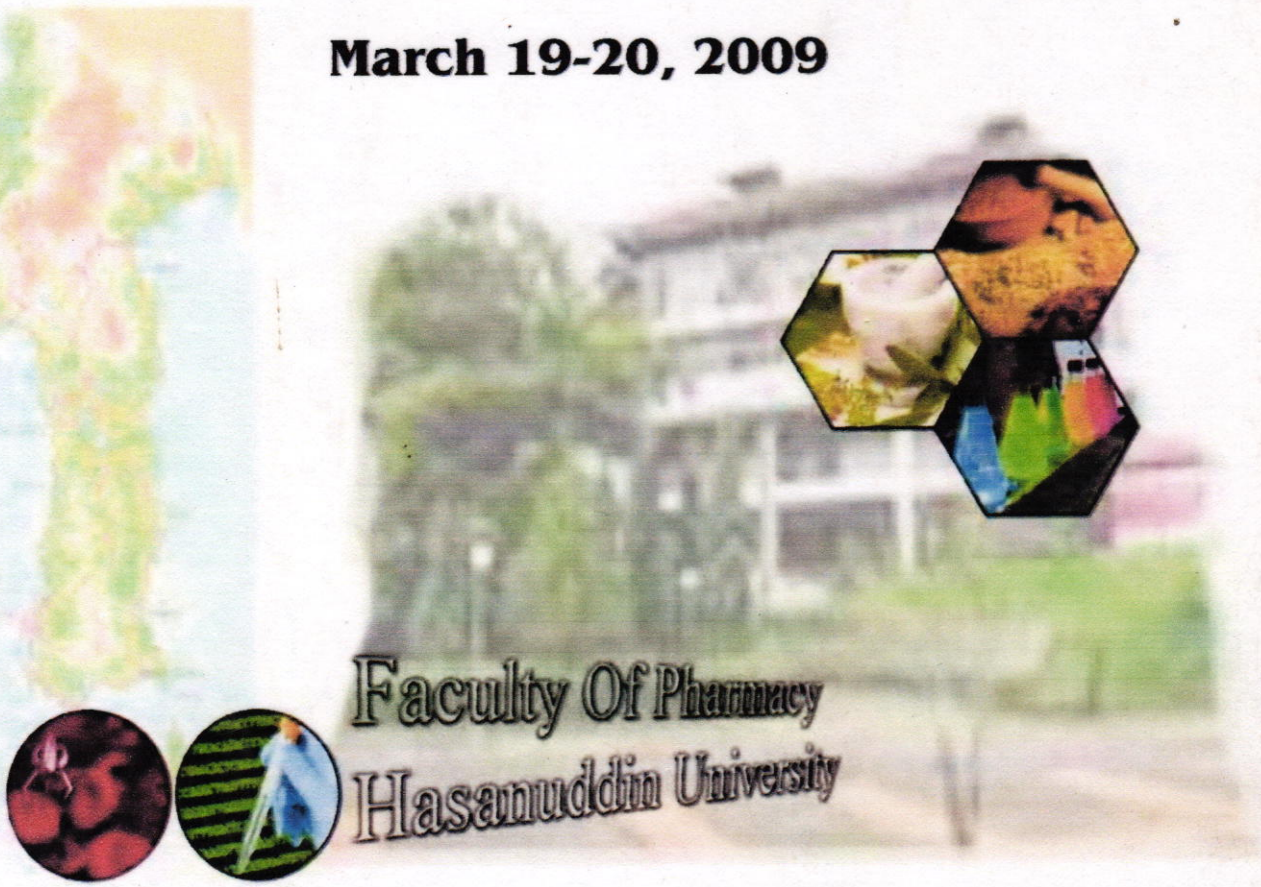
PROCEEDING OF

MAKASSAR INTERNATIONAL SYMPOSIUM ON PHARMACEUTICAL SCIENCE (MIPS)

Makassar - South Sulawesi
Indonesia

March 19-20, 2009



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MIPS 2009

Recent Progress in Drug Discovery

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Makassar Internasional Symposium
on Pharmaceutical Science
MIPS 2009

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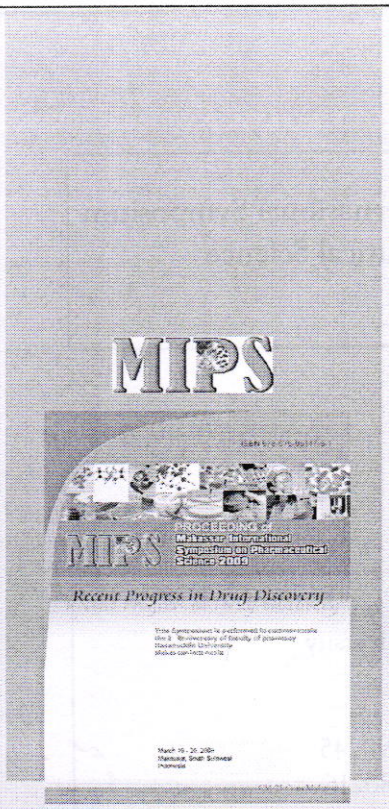

Preface From The Editor

The proceeding contains the papers to be presented at the Makassar International Symposium on Pharmaceutical Science (MIPS) to be held in Makassar during March 19th and 20th 2009.

The main purpose of MIPS was to address young scientist from locals and regions to be actively involved in drug discovery activities. The symposium celebrated the 2nd anniversary of Faculty of Pharmacy Hasanuddin University.

The symposium brought together researchers working in pharmaceutical innovation, pharmaceutical chemistry and clinical diagnostics, herbal medicine, marine natural products, pharmaceutical technology and pharmaceutical care, and included researchers from Germany, Nederland, Japan and Malaysia. Scientific reports were presented at this symposium but the full reports are available in these proceedings.

The significant aspects related to the papers included in the proceedings is a number of papers have been written by graduate students

We gratefully acknowledge the support of the participants for their verbal and written contributions. Contributions for the proceedings were sought from all participants and all papers received were carefully referred by peer reviews.

Makassar, July 2009

Marianti A. Manggau

Welcome Message on the Symposium from Dean of Pharmacy Faculty

It is great pleasure for me to be here this morning for the special event which is part of the Makassar International Symposium on Pharmaceutical Science (MIPS) and also part of the 2nd anniversary of Faculty of Pharmacy, Hasanuddin University held in Makassar 19th to 20th of March 2009.

In this symposium there are more than 71 assay, thesis and dissertations of in vitro and in vivo studies have been published, describing the Pharmaceutical Innovation, Pharmaceutical Chemistry and Clinical Diagnostic, Herbal Medicine, Marine Natural Products, Pharmaceutical Technology and Pharmaceutical Care.

We would like to thank to the national and international invited speakers, and all participants, who make this symposium possible.

Our deep appreciation to all members of the organizing committee for their great effort and time they have spent to make this meeting success. Finnaly, we hope that participants have a great discussion and we all can benefit from this symposium.

Makassar, July 2009

Elly Wahyuddin

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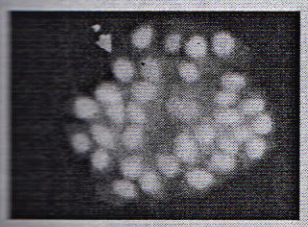

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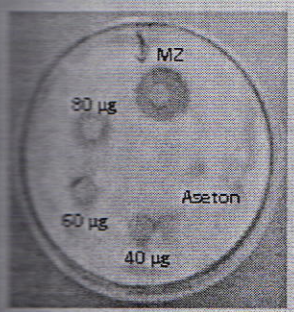

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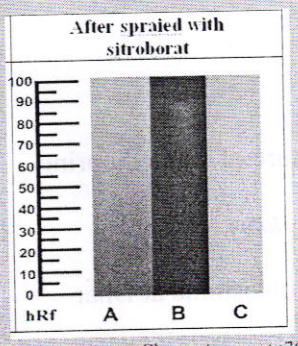

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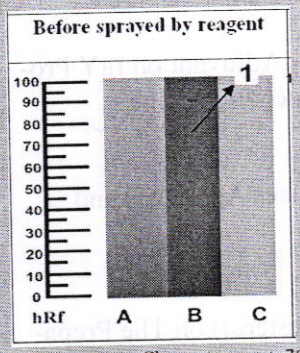

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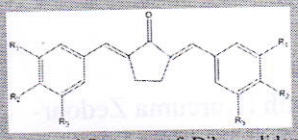

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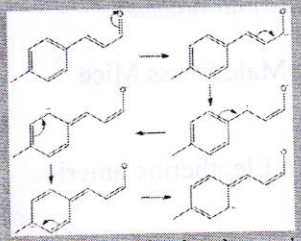

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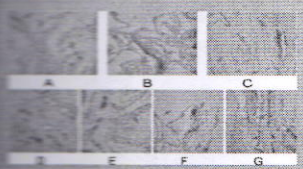

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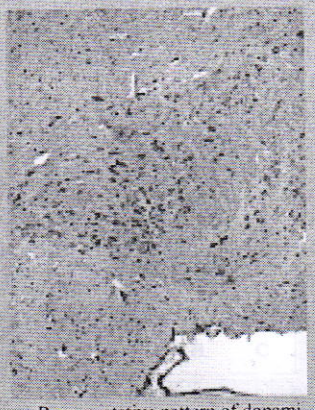

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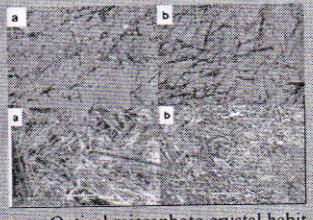

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The Influence of Niosome System (Span 20/60-Cholesterol) on The Preparation Characteristics and Released of Diclofenac Sodium from HPC: HEC Gel Based

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Department of Pharmaceutics of Faculty of Pharmacy, Airlangga University Surabaya, Indonesia

Abstract

The present study was designed to investigate the influence of niosome system (Span 20/60-cholesterol) on the characteristics preparation and diclofenac sodium released from HPC-HEC (1:1) gel based. Niosome is vesicle system was made from surfactant non ionic and cholesterol. The composition of niosome system of diclofenac sodium:Span 20/60:cholesterol was 1:6:6. Formulation of diclofenac sodium gel was formula I and II, as control of HPC-HEC gel of diclofenac sodium with Span 20 and 60, respectively. Than formula III and IV were HPC-HEC gel of diclofenac sodium that was prepared into niosome system with Span 20 and 60, respectively. The released of diclofenac from gel formulation was done by using diffusion cell and cellophane membrane. As receptor solution was phosphate buffer saline pH 7.4 ± 0.05 at temperature 37 ± 0.5°C. The parameter of diclofenac sodium released study is flux. Results were analyzed by statistic. The result of diclofenac-Span 20/60-cholesterol showed that there was a significant difference between formula II and formula IV; formula III and formula IV. The conclusion was niosome system that was formed by Span (20/60) and cholesterol in molar ratio of sodium diclofenac, Span 20, and cholesterol = 1:6:6 gave influence on the preparation characteristics and increased the released of diclofenac sodium from HPC-HEC gel based. The highest released of diclofenac sodium was from niosome system consisting of sodium diclofenac, Span 60, and cholesterol with molar ratio=1:6:6.

Keyword(s): Diclofenac sodium, niosome, released, HPC-HEC gel.

Introduction

Transdermal delivery system has been recognized as one of the routes for the administration of drug. The transdermal delivery offers several advantages over the conventional drug therapy, including avoidance of gastrointestinal irritation, elimination pass metabolism, minimization of pain, and possible sustained release of drugs. The main barrier for absorption the compound through the skin is stratum corneum. Diffusion of the drug through stratum corneum is affected by released of drug from the based. Released of drug from the based is affected by physicochemical of the drug such as solubility, partition and interaction of drug to the based. Diclofenac sodium is NSAID, the drug causes gastric irritation and undergoes hepatic first-pass metabolism (40-50%)(Ganiswara, 1995). Diclofenac sodium has log P 1.13 (Budavari et al, 2001), so it hydrophobic compound and has small solubility in water and distribution in the gel based not well. One of the method to increase distribution in the gel based by made vesicle, niosome (Choi and Maibach, 2005). Niosome is well documented for transdermal drug delivery. Niosome system is unilamellar or multilamellar vesicle where in an aqueous solution is enclosed in highly ordered bilayer made up of nonionic surfactant with or without cholesterol and dicetyl phosphate (Biju et al, 2006). The recent study, to improve the released of diclofenac, a niosome composed of Span 20/60, cholesterol was prepared. In this study, the influence of niosome system on preparation characteristics and released of diclofenac sodium from HPC-HEC gel (1:1) was evaluated.

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Materials and Methods

Materials

Diclofenac sodium was obtained as a gift sample from PT Dexa Medika, Hydroxypropylcellulose (HPC) and Hydroxyethylcellulose were purchased from PT. Tristar (Surabaya, Indonesia), Span 60 was obtained as a gift sample from PT Surya Dermato, Span 20, and Cholesterol (Sigma), KCl (E.Merck), NaCl p.a (E.Merck), $Na_2HPO_4.12H_2O$ p.a (E.Merck), dan KH_2PO_4 p.a. (E.Merck). Compound was used without mention the specification was a

pharmaceutical grade. All ingredient were used without further purification.

Preparation and characterization of niosome

Niosomes were prepared by using Reverse Phase Evaporation Technique (REV). The molar ratio of diclofenac sodium, Span 20/60 and cholesteror is 1:6:6. Drug, non ionic surfactant and Cholesterol were weighed as indicated in Table 1. Cholesterol and Span were dissolved in chloroform, diclofenac sodium in aquadest than mixed and sonification at temperature 4-5°C for 12 minutes. The mixture was added PBS pH 7.4 ± 0.05and sonification at 4-5°C for 4 minutes. Than the mixture was rotavapored at 40°C, 300 mmHg until chloroform disappeared (± 2 h) and the end evaporated at waterbath until 2 h to make the niosome system. The niosome system was analyzed for percent drug entrapment by spectrophotometric method.

Table 1. Formula of niosome system (Span 60/60-Cholesterol) in gel of HPC-HEC

	FI	FII	FIII	FIV
Dicl. Sod.	0.200 g	0.200 g	0	0
Span 20	1.2996 g	0	0	0
Span 60	0	1.6206 g	0	0
Cholesterol	1.4480 g	1.4480 g	0	0
PBS	2.8 mL	3 mL	0	0
Niosome	0	0	15.5250 g*	14.0905 g*
HPC-HEC gel	ad 20 g	ad 20 g	ad 20 g	ad 20 g

**The amount of diclofenac sodium was 0.200g, corresponding to 1% in the formulation.*

Preparation and characterization of niosome formulation

The preparation of niosome was used by Reverse Phase Evaporation Technique (Shahiwala and Misra, 2002) Preparation of HPC-HEC gel: Mixed HPC (1%) and HEC (1%) until homogen, than added aquadest to swell the polymer. After that adding propylene glycol (15%) mixed until homogen. This gel was used as HPC-HEC gel based for niosome system. The formulation of niosome system (FIII and FIV) was prepared by adding niosome system with gel of HPC-HEC (1:1) until 20 gram. As formulations control (FI and FII) were the physical mixtured of the component of niosome system with gel of HPC-HEC (1:1) until 20 gram. All the formulation of niosome in gel of HPC-HEC were prepared three times.

Determination of the entrapment diclofenac sodium in the niosome system.

The entrapment of diclofenac in the niosome system was calculated using equation 1:

$$Ep\ (\%) = \left[\frac{(Ct - Cf)}{Ct}\right] \times 100\% \quad \ldots\ldots\ldots 1)$$

Where,

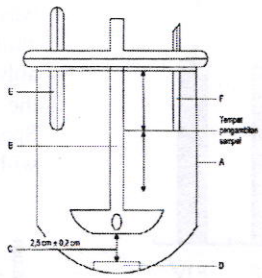
Ep : diclofenac sodium entrapment in the niosome system
Cf : concentration of diclofenac free (un entrapped)
Ct : total concentration of diclofenac sodium in the formulation of niosome system.

Determination of pH on the formulation

The pH of preparation was done by mixed the preparation in the aqua free of CO_2 in ratio 1:9. Mix well and than the pH of preparation was measured using pHmeter.

Determination of diclofenac released from the preparation.

Permeation study was performed apparatus 5 paddle over disk completely with diffusion cell (Figure 1) at 37°C for 6 h. As a membrane was cellophane and as donor compartment was filled by preparation of niosome system in HPC-HEC gel. As receptor solution was phosphate buffer saline pH 7.4. At the appropriate time sample was taken from receptor solution.



A : Diffusion chamber contain PBS pH 7.4
C : Distance from paddle to diffusion membrane
D : Diffusion cell
E : Thermometer
F : Sample holder

Figure 1. Apparatus 5-paddle Over Disk (The United States Pharmacopeial Convention, 2002)

Diclofenac concentration of sample solution was measured using Spectrophotometer. Released of diclofenac sodium was calculated using equation 2 (Higuchi, 1959).

$$Q = \frac{q}{x} = [\,Dt\,(2A - Cs)\,Cs\,]^{1/2} \quad \ldots\ldots\ldots (2)$$

Where,

Q = flux of drug released
D = coefficient diffusion of drug in the based
A = concentration of drug in the based
Cs = solubility of drug in the based
t = time

Results and Discussion

The percent entrapment of diclofenac sodium in the niosome system was shown at the Figure2. Percent efficiency entrapment although with Span 60 higher compare with that Span 20, but insignificant different.

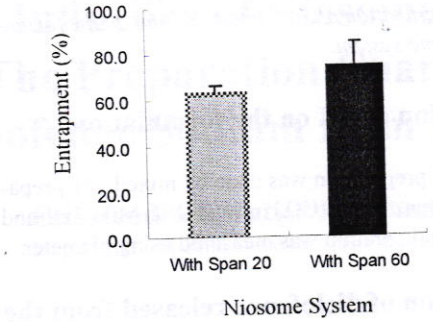


Figure 2. The diclofenac sodium was entrapped (%) in niosome system.

The pH value of FI - FIII, and FII - FIV were increased significant different. It means the niosome system increased the pH preparation (Figure 3)

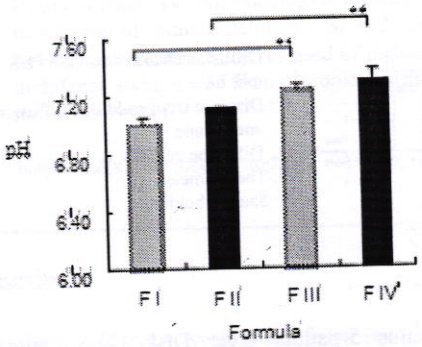


Figure 3. The pH value of the formulation

Flux is the most useful index to evaluate the released of drug. The cumulative amount of drug released was plotted as function of root time. From the result of linear regression of steady state condition I get flux at the slope. As shown in the Figure 4, the released profile shows the sufficient linearity with the coefficient r was ≥ 0.98.

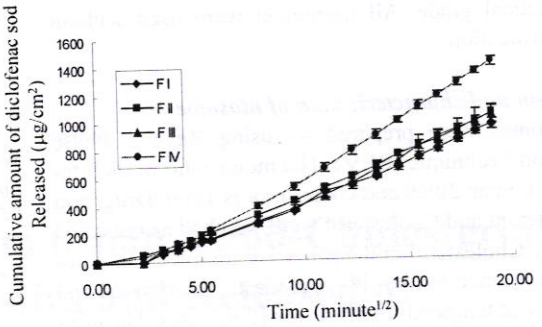


Figure 4. Released profile of diclofenac sodium through cellophane membrane in preparation of niosom system (F III and IV) and control (F I and F II) from HPC-HEC gel based.

In this Figure 5 shown the flux of diclofenac from preparation of niosom system diclofenac sodium : Span 60 : cholesterol with molar ratio 1:6:6 in HPC-HEC gel based significantly increased compared with that of control. It suggested that the niosome system increased the flux of diclofenac sodium from HPC-HEC gel based. The mechanism of increasing flux released of diclofenac sodium suggestion was the increasing solubility of drug in the HPC-HEC gel based. Flux of diclofenac sodium from niosome with composition diclofenac sodium: Span 60: cholesterol was higher compared with flux of diclofenac sodium with composition diclofenac sodium: Span 20: cholesterol probably it caused Span 60 more hydrophobic than Span 20. So, the released of diclofenac sodium in niosome system with Span 60 from the HPC-HEC based was higher compared with that Span 20.

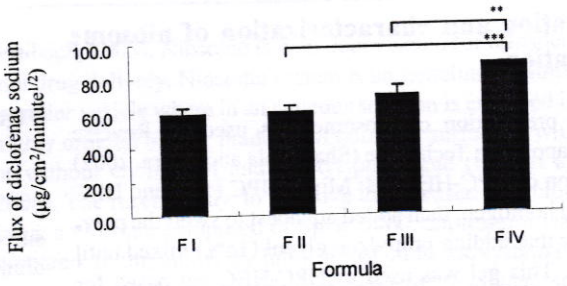


Figure 5. Flux of diclofenac sodium from preparation of niosome system in HPC-HEC gel.

Conclusions

1. The pH of the preparation of niosome system significantly increased compared with control.
2. The flux of diclofenac from FIV significantly increased compared with that FII and FIII.
3. The greater flux was observed in the niosome system of Span 60.

References

Biju, S.S., Sushama,T., Mishra P.R., Khar R.K., 2006. Vesicular Systems: An Overview, *Review Article,* Volume : 68, Issue : 2, Page : 141-153.

Budavari, S., 2001. *The Merck Index: An Encyclopedia of Chemicals, Drugs And Biological,* 13th Edition, Book 1, USA: Merck and Co., Inc, p. 3106

Choi, M. J., Maibach, H. I., 2005. Liposomes and Niosomes as Topical Drug Delivery Systems, Skin Pharmacology and Physiology 2005, *Journal of Pharmacological and Biophisiological Research, Volume 18, No.5, p.209-219.*

Ganiswara, S. G., 1995. *Farmakologi dan Terapi*, Edisi IV, Jakarta: Bagian Farmakologi FKUI, hal 207-209, 219

Higuchi, T., 1959, *Physical Chenical Analysis of Percutaneous Absorption Process From Creams and Ointments.* Presented September 23-24, 1959, Seminar, New York City

Shahiwala, A., Misra, A., 2002. Studies in Topical Application of Nisomally entrapped Nimesulide, *J Pharm Pharmaceut Sci,* **5(3):220-225.**

The United States Pharmacopeial Convention, Inc., 2002. *The Official Compendia of Standards, The United States Pharmacopeia XXV and The National Formulary XIX*, Philadelphia, p. 2011, 2018